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The Psychological Effects of Medical Research on Animal Subjects and the Ramifications for the
Applicability of the Research Results

by

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The Beginning of Animal Models

Animals are closely linked to the human society. They have always made significant contributions to our livelihood. Livestock have provided us with meat, horses the power to pull a wagon, or till a field, and farm dogs to protect our land. There is always someone walking their dog, bragging about their cat, or spoiling their animals. Our interactions with animals have shaped society. With our lives increasingly enmeshed with the lives of animals, our recognition of animal welfare has become a more informed view of how we view an animal's treatment in society. We have made substantial progress in recognizing animals as sentient beings that are capable of feeling and conscious thought. Without a voice to maintain their rights beyond a growl or bark, who is better to represent them than humans? Yet, humans have a dark history of exploiting animals.

In the Old Testament, God says that man has "dominion over the fish of the sea and over the birds of the heavens and over the livestock and over all the earth and over every creeping thing that creeps on the earth" (Gen. 1:26, *The Holy Bible: English Standard Version, Containing the Old and New Testaments* 2011). As God's people, we have "dominion" over the earth. As the majority of western civilization professes their belief in Jesus Christ, maintaining the Christian belief, animals should be viewed as a creation that merits our protection. This leaves us as the earth's stewards to protect God's creation by caring for it. While some practices reflect this responsibility, most often they do not. Our stewardship of animals has been neglected in the past. And though we have improved, the neglect has continued into the present.

Animal research has been at the forefront of the medical community for centuries. It did not begin gracefully. The French philosopher Rene Descartes' depicted animals in a way that would compel their use in the research of the human body's anatomy and physiology. This philosophical argument was seated on the idea that animals lack sentience, or consciousness, but have similar "organic" structures as humans and would be ideal research subjects. This view prompted the formation of animals as the primary resource for experiments to determine the organization of the body (Rollin 2006). In this earlier time, though now absurd, there was minimal to no concern or even proof that the animals experimented on had any fear or perception of pain and consciousness. Descartes' philosophy was typically carried out through vivisection in the 17th century. Vivisection is the dissection of a live animal without analgesics (pain medication). Descartes viewed animals as mere "machines" used to determine the body's workings (Rollin 2006). There was no protection for the animals that were under the scalpel for research. While Britain formed laws, the United States remained well behind Britain for nearly a century with regards to animal research protective laws. In 1875, the opposition to vivisection initiated an anti-vivisection Bill to the House of Lords. This bill was modified and passed by Great Britain Parliament in 1876 which came to be known as the Cruelty to Animals Act putting restrictions on the use of animals in laboratories (Rollin 2006).

The United States did not join the task force of regulating what happens behind doors in animal research laboratories until 1965, prompted by an event which made animal research hit home about the pets in families own backyards. The Lakavage family's beloved Dalmatian, Pepper, had turned up missing on a quiet night after letting her outside. She never returned. The family, devastated after hearing a neighbor had seen Pepper loaded up in an unfamiliar

truck, began a search. The family's pursuit of Pepper took them all the way to New York where it was believed she had been sold to a dealer during auction at the Green Dragon, a Chinese restaurant that sold small animals every week at an auction. Unable to gain access to the dealer, the family was in contact with Representative Joseph Resnick. The family never tired of their search for Pepper until finding that their beloved family pet had been sold to Montefiore Hospital in the Bronx New York. Pepper was a victim to an artificial pacemaker experiment and died on the operating table. She had already been cremated and the family never saw her again. Resnick led the Congress to pay attention to dog-napping situations following this incident (Engber 2014). This prompted "Peppers law", a dognapping bill later revised to "set minimum standards for the handling, sale and transport of cats , dogs, nonhuman primates, rabbits, hamsters, and guinea pigs held by animal dealers or pre-research in laboratories"(Adams and Larson 2014). This act was the building block that was continually revised to produce up to date regulations. In 1970, the AWA revised the act to cover more than just the six species from 1966 and to "regulate the treatment of *all* warm blooded laboratory animals" (Gruen 2011). The distinction that only warm-blooded animals (or endotherms) would be protected and not cold-blooded animals (or ectotherms) excludes animals that indeed experience the same stress as their endothermic counterparts.

As a student pursuing veterinary medicine, I have a very personal stake in the subject. While a Junior in my undergraduate education I was preparing veterinary school applications and looking for opportunities to broaden my experience and breadth of knowledge. I came across an employment opportunity at a medical university as a Student Research Assistant working with pregnant ewes in a Cardiac Research Center. Trained by a Certified Veterinary Technician, I

was responsible for preparing the ewes for surgery. The ewes were kept in a holding room with small runs as they awaited surgery. The research process of one ewe was as follows. On the day of a surgery a pregnant female ewe was brought to the induction room, where she was placed in a corner and given a cocktail of sedatives via her jugular vein to which point she would slump to the floor. She was then intubated (the process of placing an endotracheal tube for breathing), carried to the V trough, and hooked up to gas anesthesia. She was then tied onto the metal trough table and a jugular catheter was placed to administer intravenous fluids (IVF). Once asleep, she was sheered and scrubbed with iodine to prepare the surgery site over her abdomen where the uterus lies. Once fully prepped for surgery, the ewe would be wheeled into the surgery room. I would connect her to a pulse oximeter monitoring device to monitor her percent oxygenation in her blood, heart rate, and blood pressure. I had some experience with monitoring anesthesia through my job at a small animal veterinary clinic, but was further trained to manipulate the anesthetic parameters to keep the ewe stable throughout surgery. Once the surgeon's reached the uterus, the ewe's fetus was exposed and jugular, aortic, and ventricular catheters were placed. These would be used following the surgery to monitor blood pressure, heart rate, and flow throughout the heart to learn more about the development of the heart in the fetus. Catheters were also placed in the mother ewe for monitoring. The fetus was carefully placed back into the uterus, the abdomen sutured shut, and all the catheters were strung between the muscle and skin layer to be run through a hole in the ewes side. The bundle of catheters were secured with a pouch on the skin surface against her abdominal wall. The ewe would be wheeled to a recovery pen and given pain medication before she awoke. There she would remain for a day and then data collection would begin. The pain medication

was only prescribed for two days. In typical abdominal surgery, pain medication is given for 5 to 7 days or longer if contraindicated. Once she has been given a day to recover, she is placed in raised stocks, in a small claustrophobic room with no windows or features pertaining to the natural environment of the non-research subject ewe. The catheters are then hooked up to machines to monitor certain parameters and there she stood for the rest of her life- up to two weeks (occasionally longer).

At one point, a ewe became so stressed in her stocks, that she collapsed and died. She was taken for a “Sac Harvest”, sacrificing her for her organs, and those of her fetus to be harvested for further research use. This was the fate for all the ewes and unborn lambs whether they died from stress or were euthanized. If the ewe is alive when sacrificed, they would allow the heart to beat the blood out of her. The lambs were removed, euthanized, and harvested for their organs as well.

Though the university is following regulation, can it confidently be said that it is sufficient for the invasive procedures being performed? The studies in ewes were specifically to gain knowledge in human heart development. While it is incredibly apparent that the medical research community has made significant strides in medical research, many studies done are not applicable to human medicine due to having to make such large generalizations from a laboratory animal “model” to a human. Medicine is an intricate dance that encompasses many factors. In cardiac research with ewes (and with any animal), there are many factors that can create noise (errors) in the data alone. A stressed out ewe, will have a higher blood pressure, more circulating stress hormones which will in turn affect the amount of blood pumped per unit time. Deleterious effects to the animal’s well-being are evident in stress situations and

“include physical and physiological damage such as reduced longevity, immunosuppression [and] reduced growth rate”(King and Rowan 2005). These stress effects are transmitted to the fetus as well. Which further affects the results and its merit. Developmental psychobiology has shown that pre-natal experiences, including improper handling or consideration of mental health of a pregnant ewe, can affect the fetus’ development. Research from veterinarian Dr. Michael W. Fox contends that these experiences, whether they be stressful or pleasant, will “influence” the pre-natal animal’s physiology (Fox 2005). The stress put on the mother, reduces her ability to properly support her fetus, altering pre-natal growth and physiology. Small scale effects of stress have large impacts on the laboratory animal and research results. Researchers are well aware of the effect stress has. But changing regulation is difficult and must prove to be absolutely necessary to warrant new laws.

Regulation

Russel and Burch introduced the central guideline of animal research in 1959 as the three R’s of research. “Replacement, Reduction, and Refinement.” Replacement is just as it sounds, replacing an animal model so a sentient being is not exposed to experimentation. Reduction is defined as reducing the number of animals used to carry out research and using only the minimum necessary instead of overuse. Refinement is ensuring that when animal use is necessary, their use is regulated so it is as humane as possible (Russel and Burch 1959). This general concept for research has continued to be expanded and revised to better suit the implications of Animal Welfare in today’s society. The issue of insufficient animal welfare laws has produced a much divided population on the research front.

As previously mentioned, the passage of the AWA was critical for laboratory animal welfare and also animal welfare in other societal practices and uses. The AWA was continually revised as new knowledge came to pass. The amendments are as follows: In 1970, the AWA covered all “warm blooded laboratory animals,” animals no longer had to cross state lines to be protected by the AWA, and proper use of anesthetics during stressful and/or painful procedures was indicated. The 1976 amendment required transporters of animals to be licensed and a standard for transport was established to maintain comfort and welfare during transportation. The amendment of 1985, followed the formation of People for the Ethical Treatment of Animals (PETA) which brought the USDA more “jurisdiction over animal welfare in the laboratory”(Rollin 2006). Furthermore, Institutional Care and Use Committees (IACUCs) were formed to ensure standards of animal care. The IACUC literature is available for public reference which includes the three R’s of research. Reaching out to the public allowed the community to begin to understand what steps laboratories were taking to promote animal welfare. In 1990, shelters were required to hold animals for a minimum of 5 days to allow owners to reclaim a lost pet before it could be sold to research laboratories. The 2002 AWA amendment brought protection to rats, mice, and birds (Rollin 2006). Most recently, in 2008 , the use of companion animals(dogs and cats) in Federal Research was to be reviewed by the National Institutes of Health to drop the use of random source dogs and cats (USDA National Agricultural Library 2008).

IACUC

Every institution, university, or facility that uses animals in their research is required to have an Institutional Animal Care and Use Committee (IACUC) under the U.S. Public Health

Service Policy. IACUCs oversee and modulate research proposals and any research being done in a given institution through use of the *Guide for the Care and Use of Laboratory Animals*. The Guide is referenced by the committee for their every move in research with animals, guiding each step that is taken in order “[...]to uphold the scientific rigor and integrity of biomedical research with laboratory animals as expected by their colleagues and society at large” (Institute for Laboratory Animal Research 2008). Our society is not complacent with the care and well-being of animals; the public wants to know that the utmost care is taken for their animals. The Guide is outlined in chapters to serve the intended audience. It begins with an introduction to the language and basic principles of laboratory animal research (chp. 1), an overview of the policies and programs within the IACUC (chp. 2), housing recommendations for various species (chp. 3), veterinary care, transportation, and humane endpoints (chp. 4), and maintenance of the facilities and protection of researchers (chp. 5). This guide is the first step to beginning laboratory animal research and becomes the right hand of the researcher for reference and guidance. This guide is a valuable tool in order to uphold the ethical standards that are expected of the scientific community. Following approval of the research there must be regulations put in place to continue monitoring the animal research. The post-approval monitoring (PAM) program keeps a close eye on the research conducted to “ensure the well-being of the animals [...]and] to refine research procedures” (Institute for Laboratory Animal Research 2008). The opportunity to continually refine research protocols and procedures is part of scientific integrity. It is necessary to seek to improve the quality of life and cause less distress to an animal that is incapable of protesting their use as a research subject.

However, no matter how comprehensive regulations are, there are always non-compliance issues. In laboratory animal research, non-compliance and failure to properly care for animals within ethical standards poses an issue of scientific integrity. If an act remains un-reprimanded, it may give the impression a researcher has the right to exploit animals. The Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) is considered to be the “gold standard” of accreditation within research institutions. There is an extensive application process in order to gain this accreditation. Accreditation is a big step involved for researchers to gain regard for exceptional care of animals used in their laboratories. The applying institution must submit an application fee and a comprehensive description of its animal care and use programs. To which there will be subsequent inspection by multiple “AAALAC representatives [who will] tour the facility and prepare an evaluative report based on standards derived from the *Guide for the Care and Use of Laboratory Animals*”(Goodman, Chandna, and Borch 2015).

In a comparative study of AAALAC accredited and non-accredited institutions, noncompliance to the AWA was evaluated through citations by the USDA for Non-Compliance Items (NCIs). The institutions holding accreditation are said to be highly revered in the medical community for showing voluntary inspection of their facilities and this reverence of the AALAC title can allow the public to be misconstrued about what occurs in the laboratory. The “AAALAC accreditation and oversight process remains entirely confidential [...] preventing outside evaluations of the efficacy of the program”(Goodman, Chandna, and Borch 2015). The scientific community seems to have no qualms about accepting the AAALAC as a standard, yet little is publicly released to allow a third party’s insight. This study brings some important insight into

how accreditations should be hesitantly accepted when little is known about the process to gain accreditation. The study concluded that:

“AAALAC-accredited facilities are regularly cited for NCIs regarding federal regulations governing the welfare of the animals in laboratories... our analysis showed that AALAC-accredited facilities had significantly more NCIs than did nonaccredited facilities” (Goodman, Chandna, and Borch 2015).

Holding an accreditation is not prestigious when the institution is lacking in their compliance of regulation. Accreditation may be seen as an attempt to mask any shortcomings a laboratory may have by putting on a false face. High standards are put forth as a façade to the public to maintain approval for practices that would otherwise be disapproved. Perhaps it is advisable to be look *more* comprehensively at highly accredited facilities for they seem to be misusing their accreditation (in some instances) rather than using it to advance the ethical standards of scientific research.

Defining stress

In analyzing the use of animals in research, it becomes necessary to evaluate a major consequence of abnormal uses of these animals. Stress. Before delving into the implications of stress, the difference between stress and distress must be established. G.P Moberg presents that certain stresses are inherit to life, in that of laboratory and non-laboratory animals alike. It does not always elicit ill effects on the animal’s welfare. However, when that stress begins to affect the animal in a more permanent way, when it “truly threatens the animals well-being, then the animal experiences ‘distress’” (Moberg and Mench 2000). Similarly, the Institute for

Laboratory Animal Research (U.S.), and Committee on Recognition and Alleviation of Distress in Laboratory Animals, defines stress as a “perturbation to “physiological homeostasis or psychological well-being” and distress as a failure to return to the normal state (Institute for Laboratory Animal Research (U.S.) and Committee on Recognition and Alleviation of Distress in Laboratory Animals 2008). Both sources contend that when an organism’s homeostasis (the point at which an animal does not have to compensate for changes either internally or externally) is disrupted, the body will recognize that disruption and seek to compensate to return to a normal state. Returning to homeostasis employs numerous mechanisms such as the sympathetic nervous system which in turn affects the endocrine system, the cardiovascular system, etc. Though stress changes the body, it is not all deleterious to an organism. Some stress can cause increased function of and fitness of the body. An example of this is the up-regulation of the immune system to combat an immunological threat or the endocrine system releasing hormones in response to stress which can increase an animal’s tolerance to certain stressors.

Psychological stress can lead to altering of physiological parameters to the extent that data will be altered even if distress is not observed. Psychological stress may be prompted by habitat inconsistencies, exposure to abnormal conditions, experimental procedures, including the anticipation of a procedure through observing other animals handled (Institute for Laboratory Animal Research (U.S.) and Committee on Recognition and Alleviation of Distress in Laboratory Animals 2008). Housing can induce stress in an individual species by insensitivity to nocturnal or diurnal sleeping schedules, and the disruptions of their circadian rhythms can cause stress when the laboratory animals are experimented on in their “somnolent” times.

Animal housing not consistent with the animal's needs, provoking stress, is a constant influence on the data. Background noise, light, and "isolated environmental insults may also cause distress in some species or models" (Institute for Laboratory Animal Research (U.S.) and Committee on Recognition and Alleviation of Distress in Laboratory Animals 2008). Different species have varied needs that need to be understood to make as undisturbed a research animal as possible.

Within a laboratory, the research environment has numerous stimuli not directly related to the experiment or test itself. The "environmental noise" includes the opening and closing of doors, ventilation systems, conversations between lab employees, equipment sounds, etc. In a laboratory, noise is not necessarily a stimulus that is heard, it can be any factor affecting the production of the signal (data) produced. Excessive noise (sounds) during a bout of construction caused physiological stress as indicated by the reduced function of GLUT2, a glucose transporter in the intestine (Baldwin, Schwartz, and Hopp 2007). IACUC's should consider noise and disturbance reduction a priority in their care of the animals. A more constant experimental environment will allow for more accurate science and reduce the quantity of laboratory animals necessary for research. Those that interact more with the animals, are more aware of the stress experienced and the contribution it makes to confound the laboratory results. Those handling the animals should be in correspondence with the research committee to improve conditions if stress is indeed noted.

The Debate

Barnard and Kaufman's article "Animal Research Is Wasteful and Misleading," explicitly presents obvious faults in animal research. While Blanchard offers a rebuttal directly to Barnard et al.'s article. Barnard looks at instances in which animal research is misinterpreted and even harmful in human medicine. The development of the polio vaccine began with virus transmission into the nose of monkeys where it bound to brain tissue giving the false finding that the disease originates in the brain. However, the disease was found to truly originate in the intestine. The administration of the virus through the nose allowed the virus to travel to the brain, misinforming researchers and delaying vaccine manufacture. Some scientists feel that cancer research in mice is often for naught as they tend to carry one-hundred times the vitamin C that humans do to keep cancer away (Barnard and Kaufman 1997). Animals are used to test the efficacy of drugs to be released onto the market before their use in humans. Over half of the drugs had serious risks to human health after approval. While animal models are the standard research entity, their differences as related to humans in reactions to drugs, situations, and diseases raise serious questions about the validity of applying them to human medicine. Barnard et al, also writes, "The stress of handling, confinement and isolation alters an animal's physiology [...and] increase[s] susceptibility to infectious disease and certain tumors as well as influence levels of hormones and antibodies" (Barnard and Kaufman 1997). The stress an animal experiences throughout their research lives and in individual experiments changes the way their body will react to the research parameters.

In Balcomb et al.'s article "Laboratory Rodent Welfare: Thinking Outside the Cage," the authors take concern with the differences between a natural and an artificial environment and the way it may contribute to stress. Blanchard presents contradictory evidence to Balcombe's

statements by providing a direct critique in “Animal Welfare Beyond the Cage... And Beyond the Evidence?”

Balcombe presents evidence of empathy (the response to another individual in distress) in mice and rats, conscious pain escape, and their placement in an “unstimulating environment” in research (J. Balcombe 2010). Rodents are placed in small cage sizes with a lack of problem solving enrichment. This promotes psychological distress by failing to stimulate natural behavior. Aggression, hiding, and other stress induced behavioral factors are often observed. Blanchard affirms potential psychological distress in the laboratory, but presents conflicting evidence that cage size in mice does not necessarily contribute to the observed stress. A psychological study using an Elevated Plus Maze (EPM), which tends to cause anxiety in mice, was completed on mice in varying cage sizes. Mice housed in larger cages with regularly changed supplemental enrichment toys showed an increased anxiety in the EPM than other mice housed in the standard cages (Blanchard 2010). However, Blanchard does not address the frequent change in environment as a potential cause of the increased anxiety in mice in larger cages. The daily interaction may cause more anxiety due to the increased movement and disturbance in the cage.

Balcombe makes a claim of more aggression in smaller cages than larger. In larger cages there is an opportunity to escape from aggressive encounters which decreases fighting between rodents. However, Blanchard presents his own study that in larger cages, with rodents of mixed sex, aggression was “high and enduring” (Blanchard, Flannelly, and Blanchard 1988). Blanchard also analyzes the differences between wild type mice and the engineered laboratory mice that have been bred for certain traits conducive to experimentation such as being less

vulnerable, less disease prone, and more tolerance to stress. They are engineered to have a high tolerance for the environment they are subjected to. Thus, the applicability of studies is questioned in both cases of poor housing and genetically altered mice. In Blanchard's critique, he does not analyze the other laboratory confinement issues that Balcombe presents such as "low light conditions experienced in the wild" that have the potential to cause "retinal atrophy and cataracts" (J. Balcombe 2010). Blanchard primarily focused on the issue of cage size, though he is well aware there are multiple other factors that contribute to psychological stress in the unnatural laboratory environment.

The Stress Effect on Data

When we get stressed out, our heart rate may increase, our blood pressure will rise, pumping more blood through our bodies. Stress will activate the sympathetic nervous system, or the 'fight or flight' response. Animals exhibit this same response all too often in a laboratory setting.

The authors from the Humane Society Institute for Science and Policy evaluated 80 published studies that document the physiological stress associated with laboratory procedures. Their discussion involves extensive data on "routine" procedures such as handling, blood collection, and orogastric gavage (the process of placing a tube through the nasal cavity to the stomach to deliver substances). The serum (fluid portion of blood absent of erythrocytes) tested had concentrations of hormones including Corticosterone, and Prolactin which are both stress response regulators. These hormones were present after brief routine handling and circulated for up to an hour after a stress exposure (Balcombe, Barnard, and Sandusky 2004).

The laboratory animals “habituated” to the presence of researchers in the room, but not to the procedures themselves. Though the procedures are “routine” and familiar, it does not eradicate them as stressful situations. They further conclude that “resulting stress and distress, may introduce confounding variability to scientific data” (Balcombe, Barnard, and Sandusky 2004). Moberg’s definition of distress claims that distress changes physiological parameters and as Balcombe asserted, it alters scientific data. If the data is not valid due to extreme laboratory conditions, the applicability to human medicine, the conclusions, and the purpose of animal research studies are questioned in their value.

The psychological ramifications of stress on an individual translate throughout the whole body. A healthy mind serves a healthy body and produces reliable research results. In Poole’s article, “Happy animals make good science,” the importance of a good “state of mind” for the laboratory animal is considered. Social instability and lack of inquisitive social behavior and interaction leaves their minds bankrupt for natural interaction with members of their species. In addition, high frequency noises such as ultrasound “can be perceived by rodents, dogs, and smaller primates,” (Poole 1997) causing psychological stress from constantly hearing background noises. Furthermore improper handling, and the lack of control on the experience, all contribute to the well-being of the animal in the laboratory (Poole 1997). The amount of stress an animal experiences and their capacity to handle it is directly correlated to its mental health and the capacity to handle it. Poole writes:

“[...] what I have termed a happy animal is [one] readily able to cope with stressors to which it is subjected. Unhappy animals have to put up with distressing conditions beyond their control which result in behavioral and physiological disabilities such as permanently raised

levels of stress hormone or reduced concentrations of sex hormones and a compromised immune system. These uncontrolled variables make them unsuitable subjects for scientific studies” (Poole 1997).

Thus scientists must make every effort to keep “happy” animals not only to appease animal welfare concerns but also to ensure reputable science is practiced. It is expected that there are going to be stressful situations for the animal in the laboratory, but they should be kept to a minimum.

Future directions to improve

Animal studies are the historically preferred method to test medical knowledge and new therapeutics before their use in humans but, these studies are not immune to failure. Often only successful studies earn publication which leads readers and supporters biased to believe there is an outright success in animal research. In cancer research, rodents are the most common model for studies. Despite their frequency of use, mice do not share the same disease processes in cancer that humans do. In a study based on publication bias “animal studies seemed to overestimate by about 30% the likelihood that a treatment will be effective because negative results are often unpublished” and “little more than a third of highly cited animal research is tested later in human trials” (Mak, Evaniew, and Ghert 2014). Many of the animals used and subsequently discarded in trials were put through the stresses and rigor of research only for researchers to arrive at the end point without new medical knowledge or discoveries. In primary stroke research programs with NXY-059, a drug for ischemic stroke, was anticipated to serve as a neuro-protective agent in human stroke patients (Gawrylewski 2007). However, at the Phase III Clinical Trial, the drug failed to produce the results the animal models had

predicted. Sid Gilman, the director of the University of Michigan's Alzheimer's Disease Research Center spoke at the Joint World Congress for Stroke Research and said that, "So many agents appeared to be effective in the animal model and failed in human trials, " (Gawrylewski 2007). A drug may appear to produce astonishing scientific results that researchers tend to ecstatically publish in their hope they can to be translated to human medicine. In the instances when multiple studies fail in their translation to human medicine, animal lives were wasted. Often the animal's contribution fails to be recognized as studies inapplicable to human trials go un-published. Failed studies are not as remarkable as a successful study or drug which explains why they remain hidden. The use of animals as research subjects is then much too highly regarded when negative results are unpublished. Perhaps animal research shouldn't be the first method explored for medical knowledge? Other methods that spare animals, and are more directly applicable to human medicine should be resourced first.

The animals that are used in laboratory research are inarguably composed of cells. The interaction of the drug, disease, or variable being tested is examined pertaining to how it directly affects cells and cellular processes in an organism. If researchers are looking at cells, why not remove the animal from the situation all together and instead use living cultures? In vitro studies, the use of living cell and tissue cultures, are an alternative to using live animals for research. They can be used for screening drugs, vaccines, and antibiotics. The U.S. National Disease Research Interchange which provides human tissue for studies involving diabetes, cystic fibrosis, and many more human diseases (PETA 2015). Embryotoxicity testing was compared to that of in vivo testing (within the organism) and was found to be just as successful.

Embryonic stem cell testing is a “scientifically validated test which is ready to be considered for regulatory purposes” (Balls 2002). The use of human tissue demonstrates cancer directly related to the disease in humans. This eliminates the extra step of translating research findings from animal models to humans.

Computational strategies (in-silico) can be useful to make complicated calculations and comparisons to known substances to narrow the breadth of substances in need of being tested if they are found to have similar properties. High throughput methods, the use of a computer to process high volumes of data without human intervention. High throughput technology can elucidate how the compound works in the body including how drugs are absorbed into cells (Ranganatha and Kuppast 2012). Stephen Quake, a bioengineering professor at Stanford University, opened the Stanford Microfluidics Foundry that makes “microfluid” chips for researchers to utilize in which “more [than] a hundred cell cultures... can take place in a rubbery silicone integrated circuit the size of a quarter (Orenstein 2006). These chips are minimalistic in expense and in their upkeep. Multiple cells within the chip are available for testing allowing multiple combinations of drugs and interactions to be tested at one time. When microfluid chips become available to researchers, this new technology may reduce the number of laboratory animals needed, if not eliminate them all-together. Furthermore, the high expense that is put into laboratory animal use and care would be unnecessary, thus saving money for more medical developments. These new models to human disease may be “potentially superior to animal models, although there is as yet little to no evidence to support this view” (McGonigle and Ruggeri 2014). Computer models may have the ability to generate hypothesis and predict results based on “in silico simulation of human disease... of an

organism”(Butcher, Berg, and Kunkel 2004). This testing method would need to be built upon through an “organ-level” format with complexity increases from the bottom up (i.e. from cells to whole organs) (Butcher, Berg, and Kunkel 2004). With continued testing, these methods may become commonplace in substitute for animal models.

Yet another development are the human-organs-on-a-chip that mimic biological systems. These chips can test drugs and their use is being tested evaluated by the Food and Drug Administration before they become an acceptable route of drug development and testing. Wood asserts that “they would be more predictive than animal models, so drug failure rates would be lower (Wood 2012). Animal models represent only that animal being studied and can cause issues in the drug process by inaccurately labeling a drug as applicable to humans or even toxic when it could be of some therapeutic use in humans but is not in the particular animal model in use.

Many alternatives to the use of animals in research exist including micro-fluid chips, in-silico methods, and embryotoxicity testing. Currently, though there are regulations to the use of animals in research, there is an apparent deficiency in public knowledge of the conditions of laboratory animals that needs to be rectified. As a student of veterinary medicine and an advocate for animal welfare, I am well-aware of the issues periling the animal community. These animals span the medical, research, and philosophical communities and their use needs to be re-examined to minimize unnecessary animal suffering and exploitation. The 3Rs of research have not only changed research itself but the 3Rs themselves have changed as well to “focus on developing alternative approaches which avoid the use of animals” (“The 3Rs”).

A scientist has many ethical responsibilities to uphold in their profession which includes the broad category of animal use in research. As science progresses, so continues the progression of the reduction and removal of sentient creatures from invasive research. As research is refined using new techniques, medical and scientific knowledge will be clearer with the absence of the psychological and physical stress that is observed in animal research.

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